



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification ⁶ : C12N 15/12, C07K 14/52, C12N 15/10, C07K 16/24, C12Q 1/68, C12N 15/62, G01N 33/50, A01K 67/027</p>	<p>A1</p>	<p>(11) International Publication Number: WO 98/33917</p> <p>(43) International Publication Date: 6 August 1998 (06.08.98)</p>																												
<p>(21) International Application Number: PCT/US98/01973</p> <p>(22) International Filing Date: 2 February 1998 (02.02.98)</p> <p>(30) Priority Data: 08/795,430 5 February 1997 (05.02.97) US</p> <p>(63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Applications</p> <table border="0"> <tr> <td>US</td> <td>08/795,430 (CIP)</td> </tr> <tr> <td>Filed on</td> <td>5 February 1997 (05.02.97)</td> </tr> <tr> <td>US</td> <td>PCT/FI96/00427 (CIP)</td> </tr> <tr> <td>Filed on</td> <td>1 August 1996 (01.08.96)</td> </tr> <tr> <td>US</td> <td>08/671,573 (CIP)</td> </tr> <tr> <td>Filed on</td> <td>28 June 1996 (28.06.96)</td> </tr> <tr> <td>US</td> <td>08/601,132 (CIP)</td> </tr> <tr> <td>Filed on</td> <td>14 February 1996 (14.02.96)</td> </tr> <tr> <td>US</td> <td>08/585,895 (CIP)</td> </tr> <tr> <td>Filed on</td> <td>12 January 1996 (12.01.96)</td> </tr> <tr> <td>US</td> <td>08/510,133 (CIP)</td> </tr> <tr> <td>Filed on</td> <td>1 August 1995 (01.08.95)</td> </tr> <tr> <td>US</td> <td>08/340,011 (CIP)</td> </tr> <tr> <td>Filed on</td> <td>14 November 1994 (14.11.94)</td> </tr> </table>		US	08/795,430 (CIP)	Filed on	5 February 1997 (05.02.97)	US	PCT/FI96/00427 (CIP)	Filed on	1 August 1996 (01.08.96)	US	08/671,573 (CIP)	Filed on	28 June 1996 (28.06.96)	US	08/601,132 (CIP)	Filed on	14 February 1996 (14.02.96)	US	08/585,895 (CIP)	Filed on	12 January 1996 (12.01.96)	US	08/510,133 (CIP)	Filed on	1 August 1995 (01.08.95)	US	08/340,011 (CIP)	Filed on	14 November 1994 (14.11.94)	<p>(71) Applicants (for all designated States except US): THE LUDWIG INSTITUTE FOR CANCER RESEARCH [US/US]; 1345 Avenue of the Americas, New York, NY 10105 (US); HELSINKI UNIVERSITY LICENSING LTD. [FI/FI]; Viikinkaari 8 A, FIN-00170 Helsinki (FI).</p> <p>(72) Inventors; and (75) Inventors/Applicants (for US only): ALITALO, Kari [FI/FI]; Nyyrikintie 4A, FIN-02100 Espoo (FI). JOUKOV, Vladimir [RU/US]; Apartment 1F, 51 Massachusetts Avenue, Boston, MA 02115 (US).</p> <p>(74) Agents: GASS, David, A. et al.; Marshall, O'Toole, Gerstein Murray & Borun, 6300 Sears Tower, 233 South Wacker Drive, Chicago IL 60606-6402 (US).</p> <p>(81) Designated States: AU, CA, CN, JP, NZ, US, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).</p> <p>Published With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</p>
US	08/795,430 (CIP)																													
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<p>(54) Title: VASCULAR ENDOTHELIAL GROWTH FACTOR C (VEGF-C) PROTEIN AND GENE, MUTANTS THEREOF, AND USES THEREOF</p>																														
<p>The diagram illustrates the processing and activation of VEGF-C. It starts with the Prepropeptide (61) in the Processing compartment, which is converted to the Dimerised propeptide (58). This intermediate is then processed into the Secreted form (31) and Intermediately processed forms (15, 29, 31). The Secreted form is further processed into the Mature VEGF-C (21). The diagram also shows the acquisition of VEGFR-2 activating properties and the increase of VEGFR-3 activating properties.</p>																														
<p>(57) Abstract</p> <p>Provided are purified and isolated VEGF-C polypeptides capable of binding to at least one of KDR receptor tyrosine kinase (VEGFR-2) and Flt4 receptor tyrosine kinase (VEGFR-3); analogs of such peptides that have VEGF-C-like or VEGF-like biological activities or that are VEGF or VEGF-C inhibitors; polynucleotides encoding the polypeptides; vectors and host cells that embody the polynucleotides; pharmaceutical compositions and diagnostic reagents comprising the polypeptides; and methods of making and using the polypeptides.</p>																														

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 98/01973

A. CLASSIFICATION OF SUBJECT MATTER IPC 6 C12N15/12 C07K14/52 C12N15/10 C07K16/24 C12Q1/68 C12N15/62 G01N33/50 A01K67/027		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC 6 C07K C12N C12Q A01K G01N		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used)		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JOUKOV V ET AL: "A NOVEL VASCULAR ENDOTHELIAL GROWTH FACTOR, VEGF-C, IS A LIGAND FOR THE FLT4 (VEGFR-3) AND KDR (VEGFR-2) RECEPTOR TYROSINE KINASES" EMBO JOURNAL, vol. 15, no. 2, 1996, pages 290-298, XP002022272 see the whole document ---	1-5,7,8, 10,11, 30-34, 37-39,54
X	LEE, J., ET AL. : "vascular endothelial growth factor-related protein: a ligand and specific activator of the tyrosine kinase receptor flt4" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE USA, vol. 93, March 1996, pages 1988-1992, XP002066360 see the whole document ---	1-3,10, 11, 30-34, 37,38,54
-/--		
<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in annex.		
* Special categories of cited documents : "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "&" document member of the same patent family		
Date of the actual completion of the international search 29 May 1998		Date of mailing of the international search report 03.07.98
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3018		Authorized officer Holtorf, S

INTERNATIONAL SEARCH REPORT

Internat al Application No

PCT/US 98/01973

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 39515 A (HUMAN GENOME SCIENCES INC ;ROSEN CRAIG A (US); HU JING SHAN (US);) 12 December 1996 pages 21,34; examples 2,3,4,5,6 ---	1-3,10, 11, 30-34, 36-38, 40,54
X	LEE,J., ETAL. : "VASCULAR ENDOTHELIAL GROWTH FACTOR RELATED PROTEIN (vrp): A LIGAND AND SPECIFIC ACITVATOR OF THE TYROSINE KINASE RECEPTOR Flt4" EMBL SEQUENCE DATA LIBRARY, 10 January 1996, HEIDELBERG, GERMANY, XP002066361 ACCESSION NO. U4142 ---	55,56
X	JOUKOV,V., ET AL. : "A NOVEL VASCULAR ENDOTHELIAL GROWTH FACTOR VEGF-C IS A LIGAND FOR THE FLT4 (VEGFR-3)AND KDR (VEGFR-2) RECEPTOR TYROSINE KINASES" EMBL SEQUENCE DATA LIBRARY, 1 February 1996, HEIDELBERG, GERMANY, XP002066362 ACCESSION NO. X94216 ---	55,56
A	COHEN T ET AL: "VEGF121, A VASCULAR ENDOTHELIAL GROWTH FACTOR (VEGF) ISOFORM LACKING HEPARIN BINDING ABILITY, REQUIRES CELL-SURFACE HEPARAN SULFATES FOR EFFICIENT BINDING TO THE VEGF RECEPTORS OF HUMAN MELANOMA CELLS" JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 270, no. 19, 12 May 1995, pages 11322-11326, XP002061896 see the whole document ---	1-57
P,X	WO 97 05250 A (UNIV HELSINKI LICENSING ;ALITALO KARI (FI); JOUKOV VLADIMIR (FI)) 13 February 1997 cited in the application pages 10,13-17, 27; examples 8,9,11,14,15,19,22,27,28,29; claims ---	1-11, 30-34, 36-40, 43,53-56
P,X	JOUKOV,V., ET AL. : "PROTEOLYTIC PROCESSING REGULATES RECEPTOR SPECIFICITY AND ACTIVITY OF VEGF-C" THE EMBO JOURNAL, vol. 16, no. 13, June 1997, pages 3898-3911, XP002066363 see the whole document ---	1-5, 7-11,14, 15,20, 21, 30-34,54
3 P,X	WO 97 09427 A (GENENTECH INC) 13 March 1997 pages 3,5,9,10,11,24,25,34; example 5,7 ---	1-3,10, 11, 30-38,54
3	--- -/--	

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 98/01973

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 97 17442 A (IMMUNEX CORP) 15 May 1997 pages 3,7,8,17,19,21,24; examples ---	1-3,10, 11, 30-34, 36-38, 40,54
P,X	ACHEN, M.G., ET AL.: "VASCULAR ENDOTHELIAL GROWTH FACTOR D (VEGF-D) IS A LIGAND FOR THE TYROSINE KINASES VEGF RECEPTOR 2 (Flk1) AND vegf RECEPTOR 3 (Flt4)" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE USA, vol. 95, January 1998, pages 548-553, XP002066364 abstract, pages 548, right column, page 549, 551; figures 1 + 4; ---	1-3, 30-34
P,X	JELTSCH,M., ET AL. : "HYERPLASIA OF LYMPHATIC VESSELS IN VEGF-C TRANSGENIC MICE" SCIENCE, vol. 276, 30 May 1997, pages 1423-1425, XP002066365 see the whole document ---	1-3,10, 11, 30-32, 37-40, 53,54
T	JOUKOV,V., ET AL.: "A RECOMBINANT MUTANT VASCULAR ENDOTHELIAL GROWTH FACTOR-C THAT HAS LOST VASCULAR ENDOTHELIAL GROWTH FACTOR RECEPTOR-2 BINDING , ACTIVATION, AND VASCULAR PERMEABILITY ACTIVITIES" THE JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 273, no. 12, 20 March 1998, pages 6599-6602, XP002066366 see the whole document -----	1-57

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 98/01973

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 37-47 and 49,50,52,53 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
The polypeptide analog of claim 13 was searched as referring to the analog mentioned in claim 12.
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 98/01973

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9639515 A	12-12-1996	AU 6046796 A EP 0837934 A	24-12-1996 29-04-1998
WO 9705250 A	13-02-1997	AU 6616996 A EP 0842273 A	26-02-1997 20-05-1998
WO 9709427 A	13-03-1997	AU 7012896 A	27-03-1997
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